P. ENT COOPERATION TREAT

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 May 2000 (02.05.00)	
International application No. PCT/US99/20122	**Applicant's or agent's file reference** PENN-0698
International filing date (day/month/year) 01 September 1999 (01.09.99)	**Priority date** (day/month/year) 01 September 1998 (01.09.98)
Applicant DIAMOND, Scott, L.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 March 2000 (23.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/20122

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 38/00, 48/00
US CL : 514/2, 44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/41606 A2 (THEREXSYS LIMITED) 27 December 1996, page 4, first paragraph of summary; page 5, lines 8,9,20 and 21; page 8, line 20; page 10, lines 7-9; page 17, lines 11-13; page 20, lines 2-7; page 26, lines 16-20; page 32, lines 3-8; page 91, first full paragraph; page 92, lines 1-4 and last full paragraph; and claim 22 on page 121.	1-7, 9-14
Y	JANS et al. Signals mediating nuclear targeting and their regulation: Application in drug delivery. Medicinal Research Reviews. July 1998. Vol. 18, No. 4, pages 189-223, especially page 192, lines 1-4 of second paragraph; pages 210 and 211; Figure 2 on page 212; and paragraph bridging pages 214 and 215.	1-7, 9-14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 26 OCTOBER 1999	Date of mailing of the international search report 17 NOV 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD SCHNIZER Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/20122

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHAN et al. Mutual exclusivity of DNA binding and nuclear localization signal recognition by the yeast transcription factor GAL-4: Implications for non-viral DNA delivery. Gene Therapy. September 1998, Vol. 5, No. 9, pages 1204-1212, entire document, especially abstract.	1, 4
A	SHEN, W-C. Nuclear import of DNA: the ultimate targeting in gene therapy. Journal of Drug Targeting. 1997, Vol. 5, No. 1, pages 11-13, entire document.	1-14

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

5

Applicant's or agent's file reference PENN-0698	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/20122	International filing date *(day/month/year)* 01 SEPTEMBER 1999	Priority date *(day/month/year)* 01 SEPTEMBER 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 38/00, 48/00 and US Cl.: 514/2, 44		
Applicant THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23 MARCH 2000	13 SEPTEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RICHARD SCHNIZER Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)*

INTERNATIONAL [redacted]IMINARY EXAMINATION REPORT

[redacted]national application No.
PCT/US99/20122

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-24, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
pages 25-26, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
pages 1-4, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
pages 1-6, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [X] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/20122

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	8	YES
	Claims	1-7, 9-14	NO
Inventive Step (IS)	Claims	8	YES
	Claims	1-7, 9-14	NO
Industrial Applicability (IA)	Claims	1-14	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-7 and 9-14 lack novelty under PCT Article 33(2) as being anticipated by Therexsys Limited. (WO 96/41606)published 12/27/96.

Therexsys Limited teaches a composition comprising a cationinc peptide scaffold (NBC2, page 8, line 20), the nuclear localization targeting peptide encoded by SEQ ID NO:3 of the instant invention(M9, comprising the NLS of hnpRNP A1, see page 92, lines 3-6), wherein the scaffol and the targeting peptide are conjugated by a hydrolytic-resistant linkage (see page 92, last full paragraph). The composition is useful in methods of transferring plasmid DNA to nuclei oc cells in an individual and subsequently expressing encoded genes (see page 91, first paragraph). See also: abstract; first paragraph of summary; page 5, lines 8, 9, 20, and 21; page 10, lines 7-9; page 20, lines 2-7; page 26, lines 16-20; page 32, lines 3-8; page 92, lines 1-4; and claim 22 on page 121.

It is noted that the description discloses that the sequence of SEQ ID NO:3 is recognized by transportin, thus the compositions and methods of Therexsys limited inherently satisfy claim limitations requiring interaction of the targeting sequence and transportin.

In response, Applicant argues that the instant claims are distinct because the invention of Therexsys Limited comprises a classical NLS in addition to the required non-classical NLS. This argument is not relevant because the claims require only that the composition comprise a nonclassical NLS. There is no requirement which excludes a classical NLS from the claimed composition.

Applicant also argues that it is questionable whether the invention of Therexsys Limited could be synthesized properly, because M9 is known to form dimers. However no evidence is presented which shows that the composition could not be formed, or that it would not be functional.

Finally Applicant argues that it is unpredictable whether the invention of Therexsys would function as intended because compositions comprising classical NLSs "have not been able to get (Continued on Supplemental Sheet.)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to contain an adequate written description of treating a patient by administration of the composition of claim 9. The description is inadequate because: the state of the art of gene therapy is not sufficiently advanced to allow one of skill in the art to routinely obtain therapeutic results by delivery of DNA, and the description lacks requisite teaching or examples which would provide guidance in this respect. It is noted that the description is enabling for the use of the compositions to deliver DNA to an animal for the purpose of expressing the DNA. However this utility lacks novelty and inventive step in view of the references cited.

Applicant responds that examples 9, 10, and 11 provide details on dosage ranges, formulations, and various delivery methods for the administration of the composition to an animal. These examples are found to be enabling for the delivery and expression of DNA in an animal. However, the description provides no working example of a therapeutic effect of DNA delivery, and provides no teachings which would enable a skilled artisan to overcome the barriers to therapeutic DNA delivery which were recognized in the art at the time of filing.

Claim 9 objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not adequately described in writing, as required under PCT Rule 5.1(a)(iii), for the reasons set forth in the immediately preceding paragraph.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
plasmid across the nuclear pore of intact cells". The description at page 5, lines 20-26, states that classical NLS "have not been able to get plasmids across the nuclear pore to achieve fully efficient gene transfer with 100% transfection". This statement seems to imply that transfection is achieved with classical NLSs, but that there is room for improvement in efficiency.

For these reasons, the finding of a lack of novelty is maintained.

Claims 1, 4, 9, and 11 lack novelty under PCT Article 33(2) as being anticipated by Chan et al (Gene Therapy, 1998).

Chan teaches a method of transferring DNA to nuclei of eukaryotic cells wherein the DNA is complexed with the GAL4 protein. Gal 4 comprises a nonclassical NLS. See entire document, especially abstract.

In response, Applicant argues that GAL 4 does not comprise a non-classical NLS as defined by the description at page 8, lines 7-17. This passage provides a non-limiting definition of non-classical NLSs, and subsequently provides examples of non-classical NLSs which do not interact with proteins such as importing alpha or beta. However, neither the description nor the claims requires that this be a characteristic of non-classical NLSs, it is merely cited as a characteristic of the chosen examples.

For this reason, the finding of a lack of novelty is maintained.

Claims 1-7 and 9-14 lack an inventive step under PCT Article 33(3) as being obvious over Jans et al.

Jans suggests that polypeptides comprising SEQ ID NO:3 may be chemically crosslinked to cationic, DNA-binding proteins for purpose of delivering DNA to the nuclei of cells in a patient. See entire document, especially page 192,lines 1-4 of second paragraph; pages 210 and 211, especially lines 8-14 of first full paragraph; Fig. @ on page 212; and paragraph bridging pages 214 and 215.

In response Applicant argues that Jans does not teach chemical crosslinking of SEQ ID NO:3 to cationic DNA-binding proteins for delivering DNA to the nuclei of cells. Applicant is referred to page 211, second full paragraph, which teaches that NLSs in general may be crosslinked to cationic DNA-binding proteins, including histones and other chromatin components, for the purpose of DNA delivery to the nucleus of mammalian cells. Applicant admits that Jans defines M9 (SEQ ID NO:3) as an NLS, but argues that it can only be used in conjunction with other prNLSs. This argument is not relevant because the claims do not exclude such a composition. The claims require only that a non-classical NLL is comprised by the invention, no limitation excluding any other NLS is recited.

For these reasons the finding of a lack of inventive step is maintained.

---------- NEW CITATIONS ----------
NONE